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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
09/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/573,658	MCKERRACHER ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/28/2006,6/28/2006,5/6/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's submissions filed 7 November 2006 (35 USC 371(c)(1),(2),(4) date) are acknowledged. Claims 30-85 have been cancelled by Applicant. Claims 1-29 are pending and under examination.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 3/28/2006, 6/28/2006, and 5/6/2008 have been considered by the examiner. It is noted that the IDS of 5/6/2008 is a duplicate of the IDS filed on 3/28/2006.

Specification

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The abstract of the disclosure is objected to because it does not describe the claimed invention. The claimed invention is directed to a method of prevention or inhibition of uncontrolled proliferation of a cancer, whereas abstract is directed to pharmaceutical compositions. Correction is required. See MPEP § 608.01(b).

Claim Objections

5. Claims 17 and 28 are objected to for being exact duplicates of one another. Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of migration of a neoplastic cell and proximal angiogenesis in colorectal cancer cells, human melanoma cells, and A-172 CNS cells, *in vitro*, using a *Clostridium botulinum* C3 exotransferase fused to a cell-permeable toxin, HIV Tat domain, the fusion protein BA-05 (SEQ ID NO: 4), does not reasonably provide enablement for the prevention of uncontrolled proliferation and spreading of a generic cancer type *in vitro* or *in vivo*, the prevention of migration of a metastatic neoplastic cell of a cancer in a mammal or within a resection margin of a generic cancer type *in vitro* or *in vivo*, the prevention of growth of a tumor from a malignant cell in a host tissue of a generic cancer type *in vitro* or *in vivo*, the prevention of malignant cell migration of a generic cancer type *in vitro* or *in vivo*, the prevention of malignant cell proliferation of a generic cancer type *in vitro* or *in vivo*, the prevention of angiogenesis of a generic cancer type *in vitro* or *in vivo*, the prevention of tubular structure formation of a generic cancer type *in vitro* or *in vivo,* the inhibition of migration of a neoplastic cell and proximal angiogenesis *in vivo*, or any unspecified functional analogs of a *Clostridium botulinum* C3 exotransferase unit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method of prevention or inhibition of uncontrolled proliferation and spreading or migration of a metastatic neoplastic cell of a cancer in a mammal, tissue, or within a resection margin of a host tissue, as well as prevention of growth of a tumor from a malignant cell in a host tissue in a mammal, within a resection margin of a host tissue proximal to a site of excision or removal of a first tumor of a cancer in a mammal. The claims are excessively broad in that they read on treatment (inhibition) and prophylaxis of a genera of metastatic cancerous neoplasms in a mammalian host or tissue. The specification discloses a method for treating colorectal cancer cells, melanoma cells, and A-172 CNS cancer cells in vitro with the BA-07 fusion protein (see Example 4, p. 65; and Table 2, p. 59). The specification, however, does not teach prevention of the broad genera of cancers in a host *in vivo* or *in vitro*.

The level of skill of those in the art is high due to the unpredictable nature of tumor formation and growth, and treatment thereof. The state of the art discloses that RhoA is involved in the development of cancer (Cowsert, US Patent 5,945,290, 31 August 1999; especially column 2, lines 1-2). The '290 patent teaches that RhoA-regulated pathways can induce both cellular transformation and acquisition of metastatic phenotype in cells (p. 9537, column 2, lines 2-9). The '290 patent also teaches that Clostridium botulinum C3 exotransferase ADP-ribosylates RhoA rendering the protein inactive (column 2, lines 13-15). Wild et al., (J Biol Chem. 2001 Mar 23;276(12):9537-9542) teach that the C3 transferases, including the C3 exotransferase from *Clostridium botulinum*, are devoid of a cell entry apparatus that other toxins frequently have (column 2, first paragraph). Wild et al., also teaches *Clostridium botulinum* C3 exotransferase homologues/functional analogs from different species (p. 9540, column 1, last paragraph to p. 9541, first paragraph), which have been shown to actually induce hyperplasia of the epidermis (p. 9541, first paragraph). These teachings are echoed by Busca et al., (Mol Biol Cell. Jun 1998;9:1367-1378), in melanomas. Busca et al., teach that *Clostridium botulinum* C3 exotransferase, which inhibits Rho (abstract) and *Clostridium difficile* toxin B inactivates the Rho family of small GTP-binding proteins by UDP-glucosylation and specifically inactivates Rho (p. 1368, column 1, last paragraph).

Aullo et al., (EMBO J. 1993;12(3):921-931) teach chimeras of the Clostridium botulinum C3 exoenzyme fused to fragments of diphtheria toxin which are able to penetrate into Vero cells, using the same mechanism as diphtheria toxin (abstract). Majumdar et al., (J Biol Chem. 1998 Apr 24;273(17):10099-10106) teaches the blockage of thrombin-induced cytoskeleton rounding using the C3 exoenzyme from Clostridium botulinum in 1321N1 astrocytoma cells (abstract). Van Golen et al., (Neoplasia. 2000 Sep-Oct;2(5):418-425) teaches the inhibition of RhoC function by C3 exotransferase, which also decreased production of angiogenic factors by the HME-RhoC transfectants and the SUM149 IBC (breast cancer) cells, but did not affect the control cells (abstract). Van Golen et al., determined that the overexpression of RhoC GTPase is specifically and directly implicated in the control and production of angiogenic factors by IBC (breast cancer) cells (abstract). Park et al., teach the role of RhoA signaling pathways in angiogenesis (Circ Res. 2002 Jul 26;91(2):143-50). Park et al., also teach that HMG-CoA inhibitors interfere with new blood vessel formation in both in vitro and in vivo models of angiogenesis (p. 144, column 1, first paragraph). C3 exotoxin inactivation of Rho is taught by Park et al., in the abstract. Verschueren et al., (Eur J Cell Biol. 1997 Jun;73(2):182-7, Abstract only) teaches that invasion-bound motility of lymphocytes in T-lymphoma cells depends on a Rho-mediated signal transduction pathway (abstract). Forget et al., (Clin Exp Metastasis. 15 Sept 2002;19(1):9-15) teaches that the

expression of RhoA and RhoB decreased significantly in brain tumors and are inversely related with tumor of grade II to IV malignancy (abstract).Forget et al., suggests that because RhoA and RhoB expression levels are correlated to tumor malignancy, they may serve as novel and efficient diagnostic markers for astrocytic brain tumors of histological grade II to IV and complement currently applied histopathological analysis (abstract).

The above references teach the role of C3 exotransferase in the inactivation of Rho and demonstrate the basic importance of Rho on both cellular transformation and acquisition of metastatic phenotypes. However, these teachings cannot be rectified with the unpredictable nature of inhibiting Rho signaling pathways. For example, Cleverly et al., teach that the loss of Rho function in the thymus results in the rapid onset of aggressive thymic lymphomas (Oncogene. 2000:19:13-20, especially at p. 14, first column, second paragraph). Similarly, Moorman et al., (J Immunol. 1996 Jun 1;156(11):4146-53) used C3 exotransferase transfected into cells by a double subgenomic infections *Sindibis* virus (dsSIN:C3), which resulted in inhibition of cytokinesis within the murine lymphoma cells tested, but also resulted in multinucleated cells (p. 4150, column 2, last two paragraphs). Although Moorman et al., observed apoptosis, in C3-treated cells, the multinucleated cells were only found after dsSIN:C3 treatment (p. 4150, column 2, first paragraph). Moorman et al., also teach that cell cycle progression in the treated cells continued in spite of inhibition of cytokinesis caused by the dissolution of the actin microfilament system, which was induced by treatment with C3 exotransferase (p. 4152, column 1, first full paragraph). Moorman et al., conclude that although multinucleate cell formation and apoptosis are both mediated by the inactivation of Rho, they appear to occur independently (p. 4152, column 2, last paragraph).

The teachings of Cleverly et al., and Moorman et al., demonstrate the unpredictable nature of treatment of cells with a Rho inhibitor, such as a C3 exotransferase fusion protein. Rather than inhibiting or preventing proliferation, migration, or growth of cancer cells, the cells of Cleverly et al., rapidly transformed into an aggressive lymphoma. Similarly, rather than simply inhibiting cytokinesis, the cells of Moorman et al., formed polyploidy nuclei and not all of the cells underwent apoptosis, possibly defining a mechanism of action for the aggressive rapid onset of tumors shown by Cleverly et al.

The instant specification does not clarify or distinguish the claimed treatment from the treatment of Cleverly et al., or Moorman et al., except that a different cell-permeable vehicle is used to translocate the C3 exotransferase enzyme inside the cell. The inhibition of Rho is affected in the instant invention, as well as in the experiments of Cleverly et al., and Moorman et al., leading to contrary results. Instead of treating or preventing cancer growth or metastasis, the experiments of Cleverly et al., and Moorman et al.,

show the induction and proliferation of cancerous and pre-cancerous cells. As such, the predictability of the claimed method of prevention or inhibition of cancer growth, proliferation, and migration, cannot rely on prophetic examples or speculation. Instead, actual evidence needs to be shown in light of the clearly unpredictable results found by Cleverly et al., and Moorman et al. Normally, working examples are not required, but they are helpful in determining whether applicant has taught how to make or use the invention. However, in the instant case, working examples and data showing the actual preventative or inhibitory effects shown would be needed to overcome the prior art's teachings that inhibition of Rho by C3 exotransferase conjugates actually induce cancer. The prior art renders the administration of a C3 exotransferase enzyme unpredictable in the treatment, prevention, or inhibition of cancer.

With respect to administration, claim 12 recites that the administration is to occur by injection, topical application, or by implantation. Prophetic Example 18 of the specification teaches the coating of breast implants with the C3 fusion conjugate for implantation, such that the coating would affect the desired result through direct implantation, proximal to removed cancerous tissue. However, the breath of the claims reciting that the C3 fusion conjugate may be injected, does not differentiate local versus systemic injection. The claims may be broadly construed to read on systemic injection. It is unclear how the claimed method would work via intravenous injection or via injection at a site distant from the site of the tumor, removed tumor, or resection margins. It would require undue experimentation to test administration at sites distal to the tumor or resection margin of interest for the various genera of tumors at various dosage levels to determine whether the claimed method would work via systemic injection. It is also unclear, for example, as to whether oral administration (claim 13) would be used to treat the overarching category of "brain cancer," as defined by Applicant. The C3 conjugate would likely be absorbed by localized cells in the cheek or tongue and would not actually be transferred to the tumor site of interest. It would require undue experimentation to make and test numerous cell-membrane transport moieties that could differentiate and home to the site of specific tumors of interest, by oral administration. Further, claims 2 and 4 are drawn to the prevention or inhibition of uncontrolled proliferation and spreading or migration within a resection margin and the prevention of growth within a resection margin, respectively. The specification does not teach how one of skill in the art is to administer the C3 exotransferase fusion conjugate composition to the resection margin of a "brain tumor." The anatomical structure of the cranium impairs access to locations where tumor resection margins would otherwise be located. The claims do not recited, with any specific particularity, how the composition is to be administered to these sites. No examples of intracranial administration are taught and no examples are provided showing the results of intracranial administration to resection sites.

In the instant specification, two prophetic examples are provided regarding *in vivo* treatment, Example 18, disclosing coating a fusion protein on a breast implant, following breast cancer excision (p. 77) and treatment of healthy colon tissue after colonectomy for a colon cancer by administering a fusion protein, exemplified by BA-07, to the healthy colon tissue to "prevent" the formation of additional lesions (see Example 16, p. 76). Example 4 (p. 65) and Table 2 (p. 59) discloses a method for treating colorectal cancer cells, melanoma cells, and A-172 CNS cancer cells *in vitro* with the BA-07 fusion protein (see Example 4, p. 65; and Table 2, p. 59), but neither of these examples (or any other Example) teaches a method of treatment of these cancer types *in vivo*.

Further, claims 7 and 8 are drawn to "brain tumors" which encompass multiple tumors of non-brain origin. The specification teaches "representative examples" of "brain tumors" that include "virtually any tumor, the most common being derved [sic] from tumors of the lung, breast, melanoma, kidney, and gastrointestinal tract" (p. 39, first paragraph; also recited as paragraph 139). Applicant may act as his or her own lexicographer, but Applicant's definition of "brain tumor" as "virtually any tumor" is contrary to the definition of "brain tumor" used by those of skill in the art. It is old and well-known in the art that tumors are classified based on the site of origin (see, for example, Burger. J Neuro-Oncology. 1995;24:3-7, discussing the revision of the World Health Organization's Blue Book of tumor classification; see also, www.oncologychannel.com Classification of Cancer – Grading, Staging, published 1 September 2002, first paragraph).

There are no limitations on the type of cancer or the patient population to be treated or prevented. The use of "prevention" language indicates that patient populations "at risk of" developing cancer may be treated prophylactically in order to "prevent" the growth or spreading of tumors. However, the specification fails to provide guidance as to how the artisan could identify those "at risk of" developing a cancer or as to how any specific cancer could be prevented prophylactically. The specification fails to provide guidance as to prophylactic treatment or prevention of any cancer. Prophylactic treatment and prevention are encompassed by the claims, as written. The skilled artisan could not predictably identify all individuals who might be at risk of developing any given cancer, nor could the artisan predictably prevent or treat all such cancers. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Regarding the claimed genus of cell-membrane transport moieties, fusion protein conjugates, and "functional analogs thereof," although the Rho ADP-ribosylation activity of the claimed genus of *Clostridium botulinum* C3 exotransferase functional analogs is testable, the structure of the claimed genus of functional analogs is not taught in the specification such that one of skill in the art would understand

how to make or use a non-structurally defined cell-membrane transport moiety fusion conjugate. Claim 14 limits the polypeptidic cell-membrane transport moiety to a peptide containing (read as comprising) about 5 to about 50 amino acids. However, neither the claims nor the specification disclose any specific structure for these about 5 to about 50 amino acids. Claims 5 and 15 recite the species of BA-05, whose structure and function are taught in the specification. Wild et al., (*supra*) teaches *Clostridium botulinum* C3 exotransferase homologues from different species, several of which have Rho ADP-ribosylation activity similar to the *Clostridium botulinum* C3 exotransferase (p. 9540, column 1, last paragraph to p. 9541, first paragraph). Fawell et al., (PNAS USA. 1994 Jan;91:664-668), teach HIV Tat-mediated delivery of heterologous proteins into cells (abstract) and Vives et al., (J Biol Chem. 1997 June 20:272(50):16010-16017) teach a truncated HIV-1 Tat protein basic domain, which rapidly translocates through the plasma membrane and accumulates in the nucleus. However, the instant specification does not teach sufficient distinguishing structural characteristics to support the claims, as written. It would require undue experimentation to make the claimed genera of generic fusion conjugates recited in the broadest claims (1-4, 6-14, and 16-29) and test the same for functional activity.

Regarding the composition of the pharmaceutical composition of claims 17-29, a specific formulation of the pharmaceutical composition is not taught in the specification. It is unclear whether the structure or function of the BA-05 or any members of the genera of generic C3 fusion constructs would be adversely affected by any one or more of the recited buffer conditions, chelating agents (in particular), sugars, protein composition, stabilizers, salts, or combinations thereof, in a pharmaceutical composition. Undue experimentation would be required to make and test the claimed generic combinations of pharmaceutical compositions comprising the genera of C3 fusion constructs and test the same for activity. Additionally, it is unclear whether the C3 fusion constructs would survive the sterilization recited in claim 24, if the sterilization was conducted, for example, in an autoclave. The claim broadly reads on sterilization by any means, including heat and pressure, which would likely denature the construct.

Due to the large quantity of experimentation necessary to determine how to prevent uncontrolled proliferation and spreading of a generic cancer type *in vitro* or *in vivo*, the prevention of migration of a metastatic neoplastic cell of a cancer in a mammal or within a resection margin of a generic cancer type *in vitro* or *in vivo*, the prevention of growth of a tumor from a malignant cell in a host tissue of a generic cancer type *in vitro* or *in vivo*, the prevention of malignant cell migration of a generic cancer type *in vitro* or *in vivo*, the prevention of malignant cell proliferation of a generic cancer type *in vitro* or *in vivo*, the prevention of angiogenesis of a generic cancer type *in vitro* or *in vivo*, or the prevention of tubular structure formation of a generic cancer type *in vitro* or *in vivo*, the lack of direction/guidance presented in

the specification regarding which patient population and what therapy regimen to administer, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes that administration of C3 exotransferase fusion proteins actually induces malignancies in certain tumor types, the unpredictability of the treatment outcomes, and the breadth of the claims which read on prevention of all metastatic cancer types, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 6-14, and 16-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method of prevention or inhibition of uncontrolled proliferation and spreading or migration of a metastatic neoplastic cell of a cancer in a mammal, tissue, or within a resection margin of a host tissue, as well as prevention of growth of a tumor from a malignant cell in a host tissue in a mammal, within a resection margin of a host tissue proximal to a site of excision or removal of a first tumor of a cancer in a mammal.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111, (Fed. Cir. 1991), states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a cell-permeable fusion protein conjugate comprising a

polypeptide cell-membrane transport moiety and a Clostridium botulinum C3 exotransferase unit or a functional analog thereof.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* BA-05. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. While "examples explicitly covering the full scope of the claim language" typically will not be required, a sufficient number of representative species must be included to "demonstrate that the patentee possessed the full scope of the [claimed] invention." Lizardtech v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Although the Rho ADP-ribosylation activity of the claimed genus of *Clostridium botulinum* C3 exotransferase functional analogs is easily testable, the structure of the claimed genus of functional analogs is not adequately described in the specification, such that one of skill in the art would understand that Applicant was in possession of the genus. For example, claim 14 limits the polypeptidic cell-membrane transport moiety to a peptide containing (read as comprising) about 5 to about 50 amino acids.

Neither the claims nor the specification disclose any specific structure for these about 5 to about 50 amino acids. Claims 5 and 15 recite the species of BA-05. Wild et al., (*supra*) teaches *Clostridium botulinum* C3 exotransferase homologues from different species, several of which have Rho ADP-ribosylation activity similar to the *Clostridium botulinum* C3 exotransferase (p. 9540, column 1, last paragraph to p. 9541, first paragraph). Fawell et al., (PNAS USA. 1994 Jan;91:664-668), teach HIV Tat-mediated delivery of heterologous proteins into cells (abstract) and Vives et al., (J Biol Chem. 1997 June 20:272(50):16010-16017) teach a truncated HIV-1 Tat protein basic domain, which rapidly translocates through the plasma membrane and accumulates in the nucleus. However, the instant specification does not disclose sufficient distinguishing characteristics to support the claims, as written. The structure of the fusion conjugate in the broadest claims is not adequately disclosed.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a cell-permeable fusion protein conjugate comprising a polypeptide cell-membrane transport moiety and a Clostridium botulinum C3 exotransferase unit or a functional analog thereof. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1). The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Provisional Obviousness-Type Double Patenting Rejections

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d

887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 9-14, and 16 of copending Application No. 10/902,878. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications recite the same subject matter and substantially overlap in scope. Instant claims 1-4 and 6-8 application recite the same subject matter as claims 1 and 3 of the '878 application. Instant claims 5 and 15 correspond to claim 5 of the '878 application. Instant claims 9, 10, 11, 12, 13, 14, and 16 correspond to claims 9, 10, 11, 12, 13, 14, and 16 (respectively) of the '878 application. Additionally, SEQ ID NOs: 36 (amino acid sequence) and 56 (nucleic acid sequence) of the '878 application are 100% identical with instant SEQ ID NO: 4 (BA-05) (see search results in SCORE) (compare instant claims 5 and 15 with claim 5 an 15 of the '658 application).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1, 3, 5-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-63, 68-77, 86, 88-90 of copending Application No. 11/643,940. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications recite the same subject matter and substantially overlap in scope. Claims 60-63 of the '940 application have been amended to recite the same subject matter of instant claims 1, 3, and 5. Claim 68 of the '940 application corresponds to instant claim 10. Claim 69 of the '940 application corresponds to instant claims 9 and 11, with overlapping ranges. Claim 70 of the '940 application corresponds to instant claim 12. Claim 71 of the '940 application corresponds to instant

claim 13. Claim 72 of the '940 application corresponds to instant claim 14. Additionally, SEQ ID NO: 7 of the '940 application is 100% identical with instant SEQ ID NO: 4 (BA-05) (see search results in SCORE). Claims 73-77, 86, and 88-90 correspond to instant claims 6-8 and 17-21. Applicant is reminded that MPEP § 804 (II) states, "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure." (Emphasis added). "Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)."

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 65-67, 69-83, 86, 87, 89, and 91-94 of copending Application No. 11/808,773. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications recite the same subject matter and substantially overlap in scope. Instant claims 1-29 recite the same subject matter as claims 65-67, 69-83, 86, 87, 89, and 91-94 of the '773 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Examiner, Art Unit 1647